Kawasaki Disease Onset during Concomitant Infections with Varicella Zoster and Epstein-Barr Virus

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Kawasaki disease is an acute systemic vasculitis that predominantly affects preschool-aged children. It has a predilection to coronary arteries, and its precise etiology is still unknown. Many infectious agents, including viruses and bacteria, have been suggested as potential causes of the disease. Here, we report a patient who met the diagnostic criteria of Kawasaki disease during concomitant Epstein-Barr virus and varicella-zoster virus infections, and we discuss the possible roles of these viruses in etiology.

Key words: Kawasaki disease ■ Epstein-Barr virus ■ chicken pox

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INTRODUCTION

Kawasaki disease is a systemic vasculitis of childhood, and the most important complication of the disease is coronary artery involvement. Coronary artery aneurysms develop in 20–25% of patients. These are clinically silent and may progress to myocardial infarction and sudden death in older patients.[1] The precise etiology of Kawasaki disease is still unknown, but the environmental factors that have been considered include medications, pets, rug shampoo and immunizations.[1,2] Many infectious agents, including viruses and bacteria, have also been suggested as potential causes of the disease.[2-4] Epstein-Barr virus (EBV) in particular has been considered because of its potential effects on the immune system.[3] Varicella-Zoster virus (VZV) has been examined as another possible cause of Kawasaki disease.[4] Infections with these viruses are widely encountered in childhood, and VZV is notable for its prevention by immunization. Here, we present a patient who had the rare misfortune of meeting the diagnostic criteria of Kawasaki disease during concomitant infections with EBV and VZV.

CASE REPORT

A three-year-old boy presented with a five-day history of fever (up to 39.5°C) and an erythematous skin rash with desquamation in the perineum. The child also had a history of chicken pox, which had begun 10 days before the present hospital visit. On physical examination, his temperature was 39°C, heart rate was 105 beats/min and blood pressure was 90/60 mmHg. Several skin lesions suggesting varicella infection were present on his trunk and face. On his trunk, there were also macular erythematous lesions that did not fade with pressure. Other notable findings on physical exam included strawberry tongue, erythematous changes on the palms, extensive desquamating lesions on the perineum, bilateral nonpurulent conjunctival hyperemia, palpable lymph nodes in the cervical region (the largest was 3 cm), hepatomegaly and splenomegaly. Cardiovascular, respiratory and neurological examinations were unremarkable. Hematological findings and blood smear revealed no abnormalities except slight hypochromia and microcytosis. The erythrocyte sedimentation rate was 90 mm/hour and C-reactive protein was 197 mg/dL (normal = 0–8 mg/dL). Alanine aminotransferase was 78 U/L, aspartate aminotransferase was 321 U/L, total serum bilirubin was 4.4 g/dL, conjugated bilirubin was 2.29 g/dL and alkaline phosphatase was 798 U/L. To rule out collagen disease, tests were performed for antinuclear antibodies, anti-deoxyribonucleic acid (DNA) antibodies and double-stranded DNA antibodies, and all results were negative. Abdominal ultrasonography showed hepatomegaly, splenomegaly and marked hydrops of the gallbladder.

The patient was diagnosed with sepsis and was admitted to the hospital. For treatment, cefotaxime (200 mg/kg, intravenous) and amikacin (15 mg/kg, intravenous) were started immediately. On the fifth day of therapy, there was no change in the patient's fever or hepatosplenomegaly. At this time, laboratory examina-

tions showed an erythrocyte sedimentation rate of 150 mm/hour and a C-reactive protein level of 81 mg/dL. Bone marrow aspiration was performed to rule out hematological and lymphoid malignancies, and results for these were negative. On the sixth day, palmoplantar desquamation was observed, and the patient was considered to have Kawasaki disease. Antibiotic therapy was stopped and intravenous immunoglobulin was started at a dose of 2 g/kg over 12 hours. Within two hours the patient's fever resolved, and the erythematous skin lesions resolved within 48 hours. The hepatosplenomegaly and lymphadenopathy persisted. Acute phase reactants, serum transaminases and bilirubins returned to normal levels within three days. On the patient's 11th day in the hospital (fifth day of immunoglobulin therapy), we studied serology for EBV. Anti-EBV IgM was positive for viral capsid antigen and early antigen. On the seventh day of immunoglobulin therapy, all physical examination findings had returned to normal except the hepatomegaly and the cervical lymphadenopathy (largest measured lymph node at this time was 2 cm). Coronary arteries were normal on echocardiography. The patient was discharged, and at the three-week and two-month follow-up visits, all examinations and laboratory findings were normal.

DISCUSSION

The diagnosis of Kawasaki disease is confirmed clinically by the presence of fever for ≥5 days and the presence of four of the following five conditions, in the absence of another disease to account for the illness: 1) bilateral conjunctival injection; 2) changes of the mucous membranes of the upper respiratory tract (injected pharynx, injected, fissured lips, strawberry tongue); 3) polymorphous rash; changes of the extremities (peripheral edema, peripheral erythema, periungual desquamation); and 4) cervical lymphadenopathy.[5,6] Such clinical criteria are needed because there is no definite laboratory test for the diagnosis of Kawasaki disease. Our patient met these criteria. However, staphylococcal toxic shock, which is associated with sepsis, may mimic Kawasaki disease.[7] Toxic shock is associated with fever, hepatosplenomegaly, rash and elevated acute-phase reactants and transaminases. For this reason, our patient was treated with antibiotics until the characteristic palmoplantar desquamation of Kawasaki disease occurred and the diagnosis was revised. Desquamation in the groin and perineum can occur in either toxic shock or Kawasaki disease, so the finding of palmoplantar desquamation is important in the differential diagnosis.[7]

The etiology of Kawasaki disease remains unknown. Although its seasonal peak is in winter and spring, geographically focal epidemics suggest that infectious agents may cause Kawasaki disease.[2]

Our patient had been infected with two of these possible etiological agents, and the coexistence of VZV and EBV may have been a factor in the onset of Kawasaki disease in our patient. Some investigators advocated that none of the herpes viruses (EBV, cytomegalovirus, human herpes virus-6, varicella-zoster virus or herpes simplex virus) plays a unique or dominant role in the etiology or pathogenesis of Kawasaki disease.[8] However, many reports in the literature suggest otherwise.[1-4,9] Culora et al.[3] reported that EBV-encoded RNA was found in the myocardium and coronary artery pathological specimens of patients with Kawasaki disease.

Although not all patients diagnosed with Kawasaki disease are infected with EBV at the time of diagnosis, one path toward Kawasaki disease pathogenesis may be an abnormal immune response to EBV. For example, when a patient who has been previously infected with EBV is reinfected, Kawasaki disease might develop as a result of latent T-helper cells attacking blood vessels.[10]

Another possible mechanism is that infectious agents acting as superantigens may trigger an immunological cascade that causes the vasculitis seen in Kawasaki disease.[11] This cascade progresses with the activation of the monocyte-macrophage system; neutrophils; CD4 T-helper cells; and increased cytokines such as interleukin-2, interleukin-6 and tumor necrosis factor alpha. Finally, activated adhesion molecules, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin and P-selectin, lead to margination of monocytes, neutrophils and platelets. These cells penetrate the vascular wall due to increased vascular permeability.[11,12] The common result of this is vascular damage.

In conclusion, this patient is remarkable because Kawasaki disease onset has not been previously reported in association with concomitant EBV and VZV infections. This cooccurrence is consistent with the potential roles of these viruses in the etiology of Kawasaki disease, but the mechanisms of pathogenesis are still unclear and deserve to be investigated further.

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